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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,991	01/21/2004	Julio P. Focaracci	5280	5993

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
08/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,991	FOCARACCI ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *7-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 July 2007 has been entered.

Drawings

2. The drawings were received on 25 July 2007. These drawings are accepted.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6 and 23-32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary

The quantity of experimentation necessary to practice the full scope of the invention is great, on the order of several man-years with little if any reasonable expectation of success.

It is noted that co-applicant Julio P. Focaracci did not traverse this aspect of the rejection in the Rule 132 declaration received 13 February 2007, yet in the response of 25 July 2007, applicant now traverses this element of the rejection. As seen below, and as presented in he prior Office action, the "Predictability" of the art is such that one of skill can reasonably expect to encounter al of the factors that can and do impinge on hybridization reactions.

The claimed method is not limited to the production of any one type of array, or the binding of any one type of sequence of nucleic acid to the support. Further, the clamed method does not limit the size of the array, but fairly encompasses devices that are mesoscale. The specification is silent as to how one, for example, is to apply an adhesive to a groove and to then insert a gasket into same, all the while the dimension of the entire substrate is but a few microns in size. Further, the specification is silent as to how one is to obtain any meaningful information form an array that lacks any recognition points, and wherein the nucleotide sequences are without any value, e.g., an expressed sequence tag that is wholly uncharacterized.

Clearly, he issues are vast and would require considerable time and effort to overcome, if such is even possible. Given that the art of hybridization has been conducted for several decades, and these issues have not been overcome, there is little reason to expect that they have suddenly been overcome by the filing of the instant application, which as noted below, is void of any example- real or prophetic.

The amount of direction or guidance presented,

The guidance provided is very limited. A review of the disclosure finds numerous forward-looking statements as to what could be possible, and what one may be able of achieving, however, the specification is essentially silent as to just how any size moat in any porous material, is to be fabricated.

It is noted that co-applicant Julio P. Focaracci did not traverse this aspect of the rejection in the Rule 132 declaration received 13 February 2007.

The presence or absence of working examples

There are no examples.

Declarant/co-inventor Focaracci asserts that the application does contain examples of what can be used, not that there are examples of the claimed method. It is noted with particularity that the elected invention is not drawn to products or compositions of mater but rather, are drawn to "method for preparing a substrate for hybridization."

Declarant/co-inventor Focaracci identifies various "laser-making products" and asserts that each of the listed products "is accompanied with guidelines from the manufacturer for processing various materials." (Declaration at paragraph 7.) This argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection. It is noted with particularity that the remarks offered are conclusory in nature and void of any factual underpinning. No showing has been made that any one, much less all of the identified "laser-making products" is accompanied with guidelines. Further, no showing has been made that the guidelines, even if provided, teach how to make a moat in any and all manner of porous materials. This last aspect is of import as claims 1, 2, 4-6 and 23-32 are not limited to any particular type of "porous material," substrate, gasket materials, adhesive, or to the use of any type or combination of lasers.

In addition to enabling the making of the invention, the disclosure must also enable the use of the final product. The specification is essentially silent as to how the resultant product is to be used in a method that satisfies the utility requirements of 35 USC 101.

It appears that applicant is attempting to satisfy the requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the

written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

The nature of the invention

The invention relates to solid supports used in the production of biochemical arrays, which in turn are to be "for hybridization."

The method does not require the porous layer to be affixed to the substrate.

The state of the prior art/The predictability or unpredictability of the art

The art to which the invention relates, i.e., nucleic acid array art and hybridization art, has advanced to the point that certain problematic areas have been identified. In support of this position as it relates to the manufacture and use of oligonucleotide arrays, US Patent 6,077,674 (Schleifer et al.) addresses certain highly problematic areas:

> While in situ synthesis is a very flexible means for producing DNA arrays, the fidelity or percentage of full-length oligonucleotides synthesized within a feature on the array is less than 100 percent. An ideal array will have only full-length oligonucleotides attached to each feature. The ideal array promotes accuracy in hybridization experiments or assays or target biological materials. If the fidelity of an in situ generated array is less than 100 percent, it typically has non full-length oligonucleotides within a feature that usually consists of shorter lengths of the correct sequence, and to a lesser degree, incorrect sequences. Typical DNA coupling efficiencies are around 97 to 99 percent for the standard phosphoramidite chemistry. For oligonucleotides that are 25 nucleotides in length, these efficiencies result in only 46 to 77 percent full-length oligonucleotides contained within a feature (0.97^{25} to 0.99^{25}). This loss of fidelity can cause chemical noise in hybridization conditions. The loss of fidelity can also lead to difficulty in interpreting the data.

> Photolithography is a method used by Affymetrix in California to produce in situ arrays using procedures that are similar to those used in the semi-conductor industry. In procedure described by Fodor et al. from Affymetrix U.S. Pat. No. 5,405,783, a photo-deprotection step is used where the protecting group on the phosphoramidite is removed by exposing a photosensitive protecting group to light. Four photo masks are used to create patterns to de-protect areas of the substrate and then a nucleotide is added to these regions. This technique requires four masks for each layer of nucleotides. While this technique allows for the production of high-density oligonucleotide arrays, it is less efficient than traditional phosphoramidite synthesis chemistry. With efficiencies of about 90 to 95 percent, the percentage of full-length oligonucleotides within a feature is further reduced to about 9 to 27 percent for oligonucleotides that are 25 nucleotides long (0.90^{25} to 0.95^{25}).

Carrico, (US Patent 5,200,313) similarly identifies problematic aspects of hybridization reactions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.
At column 40 of Jones (US Patent 5,858,671) the inherent obstacle in synthesizing oligonucleotide arrays is disclosed. As stated therein, "that even if the constituent enzymatic steps approach 100% completion, incompletely processed products can accumulate to significant levels. For example, during oligonucleotide synthesis of a 70-mer, requiring 69 couplings, a 99% coupling efficiency results in only 50% of the generated oligonucleotides being full length ($0.99^{69} = 0.50$)." In the present case, applicant is claiming a product that would be the result of an infinite number of couplings, not just 69 as described above.

The breadth of the claims

The invention encompasses the production of hybridization substrates of virtually any size and dimension, ranging from mesoscale devices, which are on the order of nanometers in length and width, to substrates that are many inches or feet in length and/or width. The moat that is to be collapsed into a porous layer is not required to be affixed to the underlying support. The method requires no feedback or other forms of control so to ensure that the moat does not become a channel that bisects the array, or creates a fluid channel extending on off through the edge of the support, and through which reactants may flow away from the array on the substrate, thereby lending to erroneous results and inoperable devices.

As presently worded, the method of claims 1-5, 23, 24, 26, 28 and 29 do not require the resultant product actually comprise any array, much less an array of any particular biochemical. The specification is silent as to how one is to use a support that comprises a moat in a porous layer in a hybridization reaction when no biopolymer is present.

In accordance with claims 6, 25, and 30-32, an array is present, but the claims do not recite any limitations as to what class of compounds the array is comprised of.

5. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-6 and 23-32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

> subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-6 and 23-32 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2005/0218067 (Spearin et al.).

7. Spearin et al., paragraphs [0026], [0148] and [0149], disclose a method of manufacturing a substrate for a hybridization array. As seen therein, a laser can be used to ablate a channel in to a substrate, which can be nylon, that would surround a microarray. The aspect of the substrate comprising nylon meets a limitation of claim 1 wherein the substrate is porous, which in claim 3 further defines the porous layer as comprising nylon.

8. Spearin et al., paragraph [0052], defines the analyte as "biological macromolecule, such as a polynucleotide (including, but not limited to, DNA, RNA, cDNA, mRNA, PNA, LNA) or polypeptide, or peptide whose presence, amount, and/or identity is to be determined. A biological polymer may be used as an alternate term for a biological macromolecule. The analyte is one member of a ligand/anti-ligand pair. Alternatively, an analyte may be one member of a complimentary hybridization event."

9. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-6 and 23-32 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2005/0218067 (Spearin et al.).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-6 and 23-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,770,441 B2 (1-6 and 23-32 are) in view of US Patent Application Publication US 2004/0138155 A1 (Baird et al.).

14. Dickinson et al., teach the formation of arrays of biological members, which include nucleic acid arrays, onto a support. As seen in the figures, the array may be comprised of microparticles as well as where the binding member is affixed to the surface to the substrate (e.g., Fig. 1E and 1F).

15. As seen in columns 36-37, a preferred embodiment was the binding/hybridization between complementary nucleic acids.

16. Dickinson et al., column 27, disclose the inclusion of a gasket around the periphery of the chamber. As disclosed therein, the gasket may be affixed to the surface of the substrate or be placed into a groove formed in the substrate.

17. Dickinson et al., each of using molding so to fashion particular shapes and/or contours.

18. Baird et al., discloses using a laser so to ablate the surface of nylon, and therein create channels or conduits in a substrate.

19. It would have been obvious to one of ordinary skill in the art to have incorporated the use of a laser to ablate a porous substrate, such as nylon, and as disclosed by Baird et al., into the method of Dickinson et al., as such as being used in he same manner and achieved the same end result- the creation of a channel in the surface of a substrate. Said artisan would have been motivated to do so as such would have reduced, if not eliminated, the need to do heating and molding of the substrate so to create a specific surface feature. In view of the laser being used in the same manner, and resulting in the same form of end product, the ordinary artisan would have had a most treasonable expectation of success.

20. For the above reasons, and in the absence of co0nvincign evidence to the contrary, claims 1-6 and 23-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,770,441 B2 (1-6 and 23-32 are) in view of US Patent Application Publication US 2004/0138155 A1 (Baird et al.).

Conclusion

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Bradley L. Sisson/ whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

23. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner
Art Unit 1634

BLS